

Syntheses and Bioactivities of Targeted and Conformationally Restrained Taxol Analogs

by

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Abstract

Taxol (**1**) was first isolated from the bark of the Pacific yew about 35 years ago by Drs. Wall and Wani. Although its development as an anticancer agent was delayed by numerous reasons, including its scarcity and insolubility, the discovery of its tubulin-assembly activity and other factors motivated oncologists to overcome these problems. It has since become one of the most important current drugs for the treatment of several cancers, including breast and ovarian cancers.

Like almost all anticancer drugs taxol does have some toxic side effects and many tumors also show significant resistance to therapy with taxol. Drug targeting studies aimed at improving its selectivity and efficacy is described. Two targeting methods, the estrogen receptor (ER) directed targeting and colloidal gold (cAu) directed targeting, were used in our research. In this dissertation, a series of estradiol-taxol conjugates (ETCs) were synthesized. They were active in four cytotoxicity assays and tubulin polymerization assay, but less active than taxol. One of them showed the desired selectivity for ER positive cancer cells.

Recently, several studies have attempted to elucidate the bioactive binding conformation of taxol on microtubules. Three models have been proposed for this conformation. The T-taxol conformation was proposed by Dr. Snyder based on electron crystallographic density and molecular modeling. In this dissertation, a series of cyclopropyl-containing taxol analogs and macrocyclic taxol lactones were synthesized. The bioassay results showed they are less active than taxol. The molecular modeling studies suggested that the cyclopropyl-containing taxol analogs could not adopt the T-taxol conformation, which would result in the loss of bioactivities. It is an indirect evidence to support T-taxol conformation. As for macrocyclic taxol lactones, it is proposed that they would have a close contact between the ester moiety on the C-3' phenyl ring and Phe272 of the β -tubulin protein when they adopt T-taxol conformation. It will push the macrocyclics out of the binding pocket and lead to the loss of bioactivities.

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List of Abbreviations

CAN	=	Ceric ammonium nitrate
10-DAB	=	10-Deacetylbaaccatin III
DCC	=	Dicyclohexyl Carbodiimide
EDC	=	1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
DMF	=	<i>N, N'</i> -Dimethylformamide
PMP	=	<i>para</i> -Methoxyphenyl
LHMDS	=	Lithium hexamethyldisilazide
RCM	=	Ring-closing metathesis
TIPS	=	Triisopropyl
TBS	=	<i>tert</i> -Butyldimethylsilyl
TES	=	Triethylsilyl
DMS	=	Dimethylsilyl
Bn	=	Benzyl
Bz	=	Benzoyl
DMAP	=	4-Dimethylamminopyridine
4-PP	=	4-Pyrrolidinopyridine
THF	=	Tetrahydrofuran
MAP	=	Microtubule associated protein
SAR	=	Structure activity relationships
ER	=	Estrogen receptor
ETC	=	Estradiol-taxol conjugate
PTLC	=	Preparative thin layer chromatography
TLC	=	Thin layer chromatography
LAH	=	Lithium aluminum hydride
cAu	=	Colloidal gold nanoparticles